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Amino acid-derived *trans*-*N*-chloroformylimidazolidinones: scalable, stereoselective synthesis, structure, and utility

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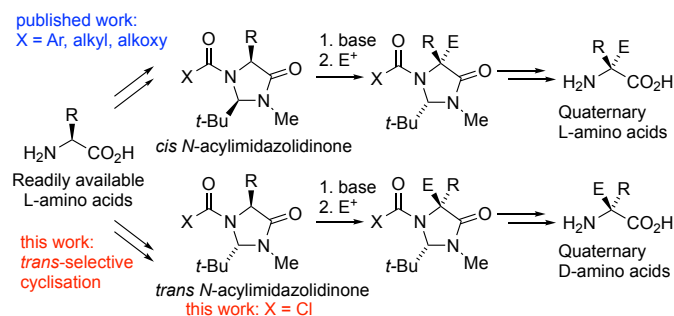
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N-Acyl imidazolidinones, which are key intermediates in the stereoselective synthesis of amino acids by 'self-regeneration of stereochemistry' methods, are classically made by only moderately diastereoselective methods. We now report that cyclisation of pivaldimino-amides with phosgene in the presence of pyridine may be made fully diastereoselective for the *trans*-*N*-chloroformylimidazolidinones, and we detail the conformational features of the products. We show that despite the presence of the electrophilic carbamoyl chloride function, the products show remarkable stability, and may be deprotonated to form enolates with useful reactivity for the synthesis of amino acid derivatives.

Introduction

Several strategies for the synthesis of quaternary (α,α -disubstituted) amino acids entail the alkylation of the α -carbon of a readily available (and therefore usually L) amino acid.^{1–5} 'Memory' of the configuration at the α -centre that is lost during the formation of the intermediate enolate may be ensured in a number of ways,^{6–9} but the most practical and widely used method, originally developed by Seebach et al.,¹⁰ employs an imidazolidinone derivative containing a second stereogenic centre that directs a subsequent alkylation step (Scheme 1). Termed 'self-regeneration of stereochemistry', this method requires a diastereoisomerically pure imidazolidinone intermediate of either *cis* or *trans* relative stereochemistry if the enantiopurity of the product amino acid is to be maximised. Methods for the synthesis of both *cis* and *trans* imidazolidinones are reported, but neither are fully diastereoselective:¹¹ classical applications of Seebach's method require crystallisation of the imidazolidinone to remove the unwanted diastereoisomer.¹² Which diastereoisomer of the intermediate is used determines the overall outcome of the reaction: the *cis* diastereoisomer retains the configuration of the original stereocentre while the *trans* diastereoisomer inverts it. Imidazolidinones have also found widespread use as organocatalysts for a wide range of reactions.^{13,14}

Scheme 1: Imidazolidinones as intermediates in the synthesis of quaternary amino acid derivatives



Diastereoselectivity may be achieved because the *trans* imidazolidinone is formed under kinetic conditions, while the *cis* imidazolidinone is thermodynamically more stable.^{11,12} We now report in full our investigation of the cyclisation of an imine precursor with a phosgene source, which demonstrates that careful choice of solvent and conditions allows the fully diastereoselective synthesis of a *trans* imidazolidinone. The *trans* product carries an *N*-chloroformyl substituent (Scheme 1, X = Cl) that may be readily converted to other functional groups, but also shows remarkable stability to basic conditions. We also report in full our investigation of the alkylation of the nucleophilic enolate derivatives of these simultaneously electrophilic species.

We have recently described several reactions in which the *N*-chloroformyl derivative of an imidazolidinone plays a pivotal role,^{15–18} and this work showed that the two diastereoisomers of these carbamoyl chlorides displayed very different reactivity. In one particular family of Bischler-Napieralski-like cyclisations,¹⁶ only the *trans* isomer was of use. We thus set out to discover conditions for the general, stereoselective synthesis of *N*-chloroformylimidazolidinones as their *trans* isomers.

Results and Discussion

Initial work was carried out using the L-phenylalanine pivaldimine derivative **1a** as our starting material. Diastereoselectivity in the formation of the *N*-chloroformylimidazolidinone **2a** from **1a** and a phosgene source was explored using the conditions shown in Table 1.

Treating **1a** with phosgene (2.5 equiv.) in dry toluene provided the product **2a** with excellent diastereoselectivity (Table 1, entry 1), but in only 40% yield after 18 h at 60 °C. Higher temperature (entry 2) only served to reduce yield and selectivity. Diastereoselectivity was maintained and the yield improved slightly in dry dichloromethane at rt (entry 3), while in THF the yield increased significantly, but at the expense of diastereoselectivity (entry 4). Acetonitrile and dioxane provided no improvement in yield or diastereoselectivity (entries 5, 6), and the alternative solid chloroformylating agent triphosgene gave almost no product (entries 7, 8).

Table 1: Trans-selective synthesis of *N*-chloroformylimidazolidinone **2a**

Solvent	Base	T / °C	yield /%
			dr ^a

1	toluene	-	60	40	95:5
2	toluene	-	100	20	57:43
3	CH ₂ Cl ₂	-	rt	48	96:4
4	THF	-	rt	70	91:9
5	MeCN	-	rt	35	80:20
6	dioxane	-	rt	37	94:6
7	CH ₂ Cl ₂	^b	rt	trace	81:19
8	CH ₂ Cl ₂	^b	40	trace	54:46
9	CH ₂ Cl ₂	Et ₃ N	rt	0	-
10	CH ₂ Cl ₂	2,6-lutidine	rt	trace	37:63
11	CH ₂ Cl ₂	DMAP	rt	32	85:15
12	CH ₂ Cl ₂	NaHCO ₃	rt	49	96:4
13	CH ₂ Cl ₂	K ₂ CO ₃	rt	26	93:7
14	THF	py	rt	nd	70:30
15	THF	py ^c	rt	78	99:1
16	THF ^d	py ^c	rt ^e	86	99:1

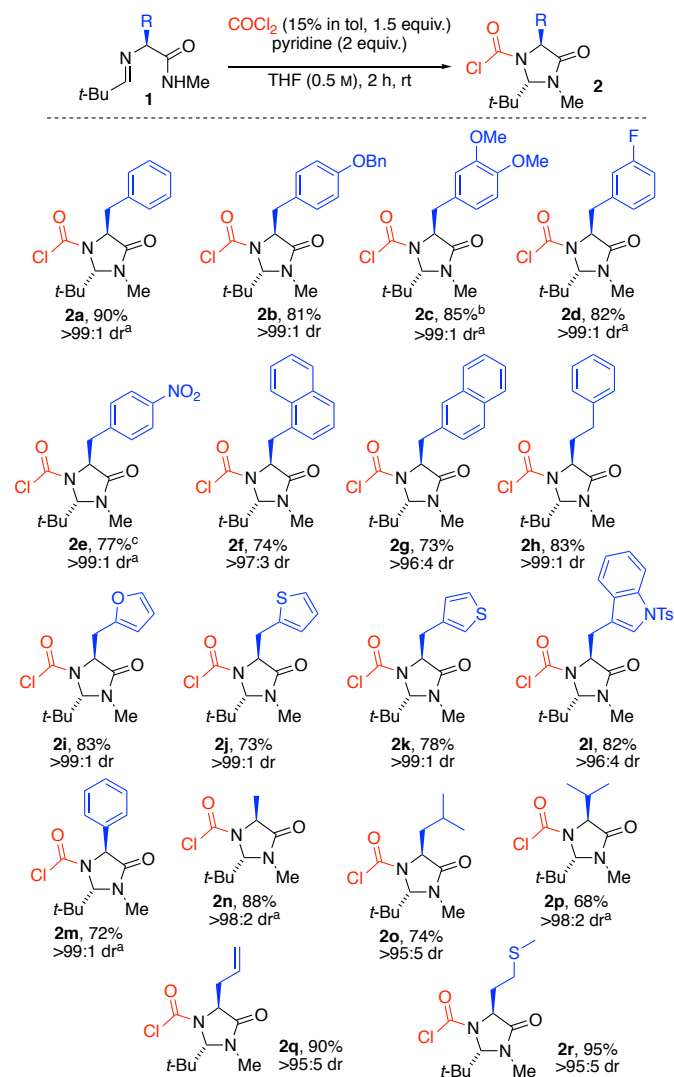
^aRatio of *trans*:*cis* in ¹H NMR spectrum of crude reaction mixture. ^bUsing triphosgene ([Cl₃CO]₂CO, 0.5 equiv.) in place of phosgene. ^cSlow addition of COCl₂; pyridine added after 2 h. ^dReaction carried out at 0.5 M. ^eFor 2.5 h.

During reactions with phosgene (entries 1-6) in toluene, dioxane, THF or MeCN, a white precipitate started to form after 10 minutes; in dichloromethane, similar precipitation occurred after 15 min, but the precipitate redissolved after a further 15 min. The precipitate formed during the reaction shown in entry 3 was isolated by filtration and characterised as the pure *trans* imidazolidinone hydrochloride salt **3a**, using NOE studies to establish relative configuration.

Conditions were explored with the aim of retaining the *trans* selectivity of the cyclisation but avoiding the reduced yield that inevitably arises from precipitation of the hydrochloride salt. Triethylamine, lutidine, and DMAP (entries 9-11) returned very poor yields of product, as did inorganic bases (12-13), albeit with improved diastereoselectivity.

An alternative approach was tried, using THF to encourage precipitation of the hydrochloride salt, but neutralising with pyridine. A significant dependence on the timing of the addition was noted: when the pyridine was added at the start of the reaction (entry 14), selectivity was poor, but when the pyridine was added after 2 h (to allow precipitation of the diastereoisomerically pure hydrochloride salt), selectivity was excellent. Optimal conditions were found when the phosgene was added slowly (entry 15), and the yield was maximised to 86% of essentially pure (99:1) *trans*-diastereoisomer by conducting the reaction at 0.5 M (entry 16). These optimal conditions proved general for a wide range of amino acid substrates, with only 1.5 equiv. phosgene required for good yields on larger (>10 g) scales. A series of pivaldimine derivatives of the amino acid *N*-methyl amides **1** gave the imidazolidinones **2a-2r** from aromatic, heteroaromatic and aliphatic amino acids (Scheme 2). Diastereoselectivity was in every case excellent, and the *trans* relative configuration of several of the products was confirmed by X-ray crystallography: Figure 1a-d illustrates the X-ray crystal structures of **2a**, **2p** and **2c**.

Scheme 2. Diastereoselective cyclisation of amino acid pivaldimines **1 to *trans*-*N*-chloroformylimidazolidinones **2**.**



^aRelative configuration confirmed by X-ray crystal structure: CCDC deposition numbers **2a** 1899271; **2c** 1871268; **2d** 1899274; **2e** 1899273; **2m** 1899272; **2n** 1899277; **2p** 1899276. ^bon 25 g scale; ^con 5 g scale.

We had previously noted that the *trans* diastereoisomers of the carbamoyl chlorides **2** were significantly less reactive than their *cis* epimers,¹⁵ presumably because of steric encumbrance to attack on either face of the chloroformyl group. This steric hindrance also led to characteristic features in the ¹H NMR spectra of **2** (and of their derivatives **3** described below). Typically, two complete sets of signals were observed, corresponding to the two rotamers about the hindered, amide-like N–CO bond. In the case of **2c**, these two rotamers were identifiable in the X-ray crystal structure (Figure 1c and 1d). The signals corresponding to the rotamers of **2p** coalesced at temperatures above 25 °C, and variable temperature NMR of **2p** in d₈-toluene (Figure 1e) allowed us to determine a barrier to conversion of the major to the minor rotamer of 63.4 kJ mol^{−1} at 300 K by modelling the exchange-broadened line shapes (Figure 1g). The more hindered carbamoyl chloride derivative of isovaline **3d** (formed by the method described below) also showed two rotamers in its NMR spectra (Figure 1f) which coalesced at a higher temperature. Line shape modelling (Figure 1h) gave a correspondingly higher barrier to conversion of the major to the minor rotamer of 71.7 kJ mol^{−1} at 300 K.

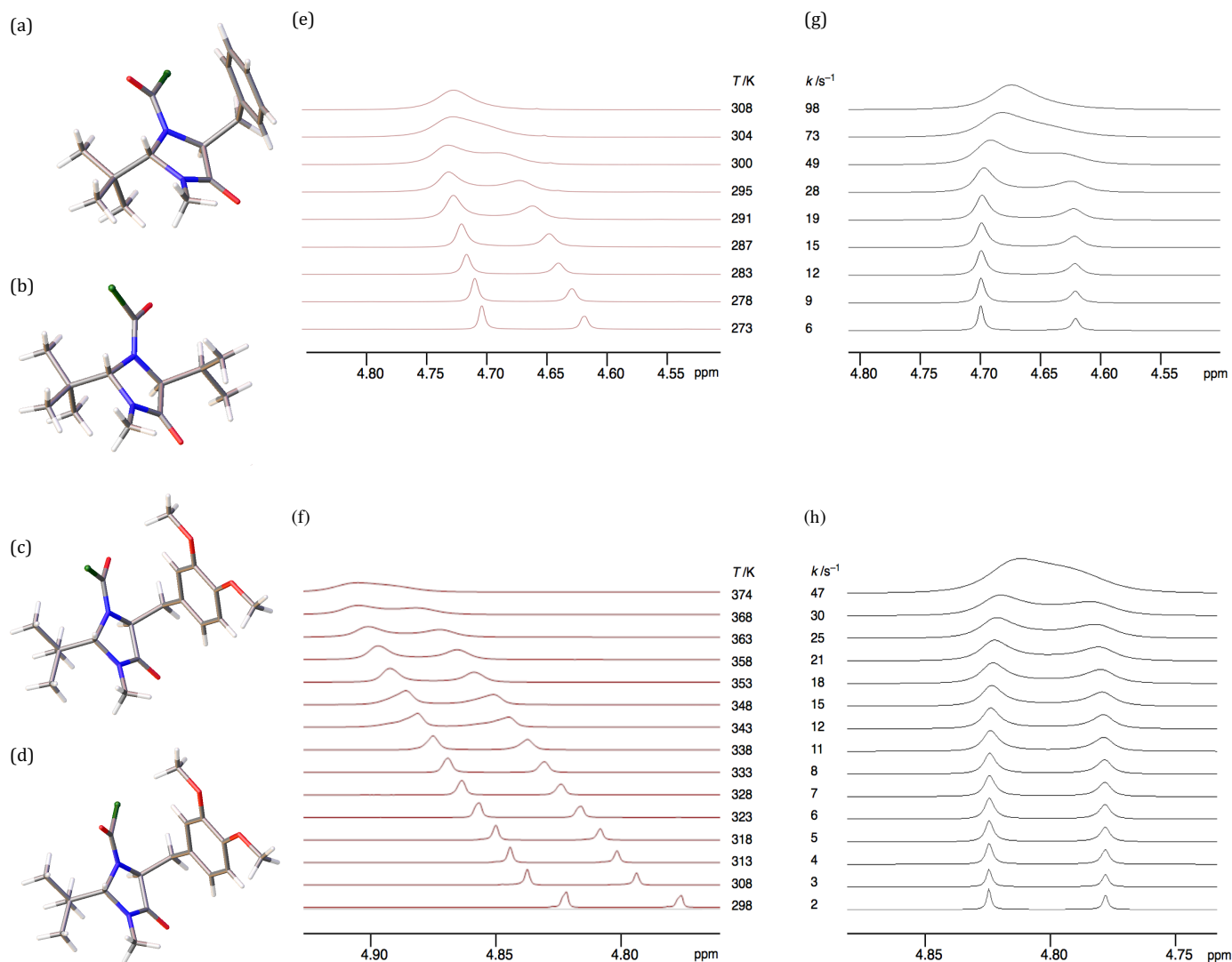
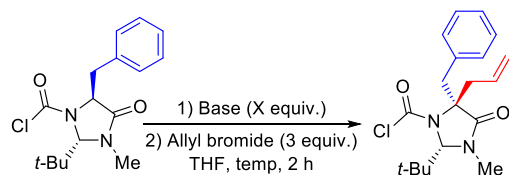


Figure 1: Stereochemistry and structure of *N*-chloroformylimidazolidinones. X-ray crystal structures of (a) **2a**; (b) **2p**; (c) **2c** (major conformer); (d) **2c** (minor conformer); Portion of the ¹H NMR spectrum of (e) **2p** in d₈-toluene between 0 and 35 °C (showing coalescence of the two N-CO rotamers populated in a 60:40 ratio); (f) of **3d** in d₈-toluene between 25 and 96 °C (showing coalescence of the two N-CO rotamers populated in a 55:45 ratio); Modelled line shapes for exchange rates indicated of (g) **2p**; (h) **3d**.

The remarkable stability of the carbamoyl chlorides **2** permitted them to be very readily isolated and purified by chromatography on silica, and suggested that despite their electrophilic reactivity it might nonetheless be possible to deprotonate them to form an enolate.¹⁸ In initial investigations, **2a** was treated with base at room temperature and quenched with allyl bromide, but only decomposition was noted with LDA, KHMDS or LiHMDS (Table 2, entries 1-3). With LDA (2 equiv.) at lower temperature -100 °C with **2a**, promisingly the alkylated product **3a** was formed only in 20% yield (entry 4). Changing the base to KHMDS at -78 °C gave **3a** successfully in excellent yield (entries 5, 6). Improved yield was ensured by minimising KHMDS equivalences (1.2 equiv.) at -78 °C. Using these conditions, the enolates from several imidazolidinones **2** were alkylated diastereoselectively to form stable, isolable *N*-chloroformylimidazolidinone derivatives

of quaternary amino acids **3**, as shown in Scheme 3. **3b** was formed from the *cis* diastereoisomer of the imidazolidinone *cis-2b*.¹⁵ The relative stereochemistry of the products **3d** and **3g** were confirmed by NOE (See Supporting Information).

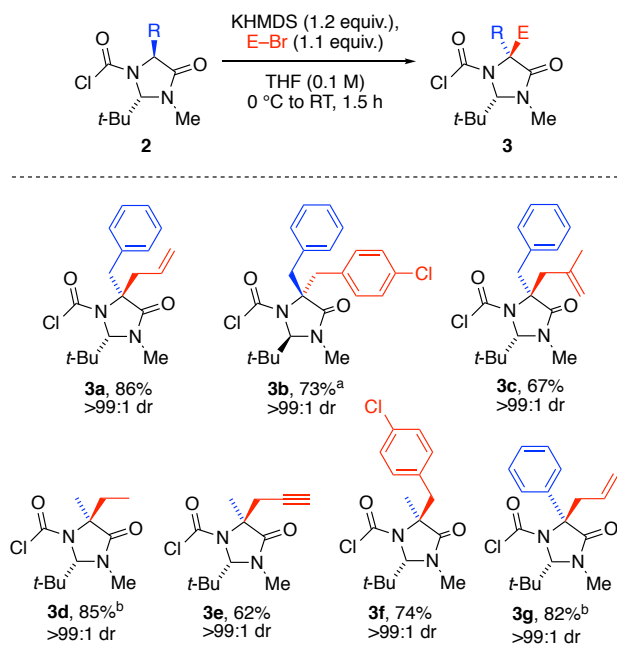
Table 2: Diastereoselective alkylation of *trans*-*N*-chloroformylimidazolidinones **2a**



2a		3a		
Entry	Base	Equiv.	T / °C	Yield (%), dr
1	LDA	2 eq.	rt	o ^a
2	KHMDS	1 eq.	rt	o ^a
3	LiHMDS	1 eq.	rt	o ^a
4	LDA	2 eq.	-100	20, >95:5
5	KHMDS	2 eq.	-78	80, >95:5
6	KHMDS	1.2 eq.	-78	86, >95:5

^aDecomposition.

Scheme 3. Diastereoselective alkylations of *trans*-*N*-chloroformylimidazolidinones **2.**

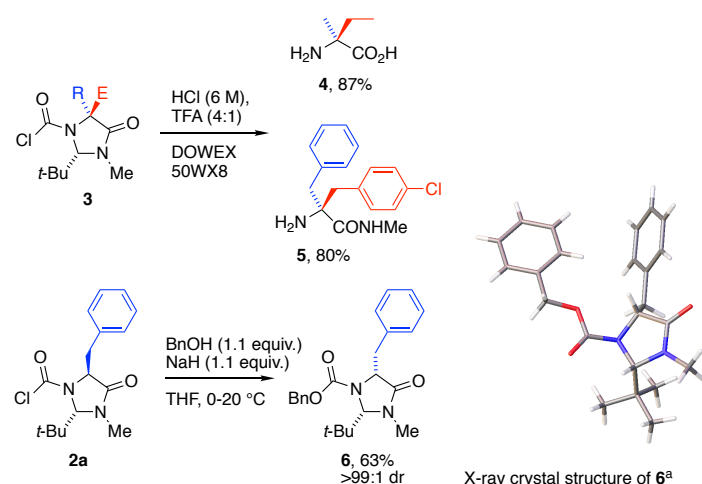


^aFrom the *cis* diastereoisomer of **2b**. ^bRelative configuration confirmed by NOE.

The diastereoselective alkylation of the carbamoyl chlorides **2** provides an alternative to the use of *N*-acylated imidazolidinones in classical 'self-regeneration of stereocentres' chemistry, but with a more readily removed nitrogen substituent. The alkylated products **3** were readily hydrolysed to the quaternary amino acids or their *N*-methyl amides, as shown for **3b** and **3d** in Scheme 4. **4** is the fungal metabolite L-isovaline, and its absolute configuration was confirmed by comparison of its optical rotation with the literature value.¹⁹

Imidazolidinones are also well established as organocatalysts.^{13,14} The diastereoisomerically pure *trans* *N*-chloroformylimidazolidinone **2** could be converted to *cis* Cbz derivative **6**, an organocatalyst precursor.^{20,21} The use of the benzyloxide anion entails epimerisation of the amino acid centre, giving from L-phenylalanine the diastereoisomerically pure *cis* imidazolidinone derivative of D-phenylalanine **6**. The relative stereochemistry of **6** was determined by X-ray crystal structure (Scheme 4).

Scheme 4: Transformations of the *N*-chloroformyl group.



^aCCDC deposition number for **6**: 1899275.

In summary, we show that cyclisation of the pivaldimine derivatives of natural amino amides using phosgene in THF in the presence of pyridine allows fully diastereoselective formation of carbamoyl chloride derivatives of *trans* imidazolidinones. These have sufficient reactivity to be converted to carbamate protected derivatives, but also display remarkable stability, allowing the carbamoyl chlorides themselves to be used as intermediates in amino acid synthesis.

Experimental Section

General Information

Where specified, reactions requiring anhydrous conditions were performed under dry nitrogen or argon atmospheres in glassware that was dried using either a combination of vacuum and heat gun, oven, or flame drying. Reaction mixtures were stirred magnetically. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula into the reaction vessels through rubber septa. All reagents were purchased at highest commercial quality and used as received (unless specified otherwise). Solvents were purchased at the highest commercial quality and used as received (unless specified otherwise). Anhydrous CH₂Cl₂, Et₂O, THF and MeCN were collected under argon from an Anhydrous Engineering alumina-column drying system. Anhydrous pyridine stored over 3 Å molecular sieves was purchased from Acros. All reaction temperatures described below –10 °C were achieved using acetone/dry ice cooling baths.

Analytical Information

R_f: TLC was performed on aluminium backed silica plates (0.2 mm, 60 F₂₅₄) which were developed using standard visualising agents: UV fluorescence (254 & 366 nm), phosphomolybdic acid, vanillin, potassium permanganate and Seebach stains.

Chromatography: Flash chromatography was performed on an automated Biotage Isolera Spektra Four using gradient elution on pre-packed silica gel Biotage SNAP Ultra columns.

mp: Melting points (mp), expressed in °C, were measured on a Kofler hotstage melting point apparatus and are uncorrected.

IR: IR spectra were recorded from neat compounds applied as thin films on a Perkin Elmer (Spectrum One) FT-IR spectrometer (ATR sampling accessory). Only absorbances of interest (ν_{\max} expressed in cm^{-1}) are reported. In situ IR measurements were performed using a Mettler Toledo ReactIR 15 instrument equipped with a 6.3 mm AgX DiComp probe and iC IR software.

NMR: Spectra were recorded on Varian VNMR (400 MHz or 500 MHz) instruments, and Bruker Ultrashield (400 MHz or 500 MHz) spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of trimethylsilane. Spectra were calibrated using the residual solvent peaks for CDCl_3 (δ_{H} : 7.26 ppm; δ_{C} : 77.16 ppm) or CD_3OD (δ_{H} : 3.31 ppm; δ_{C} : 49.00 ppm) as appropriate. Coupling constants (J) are rounded to the nearest 0.1 Hz. Splitting patterns are abbreviated to: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br.) or some combination thereof. 2D NMR experiments COSY, HSQC and HMBC were used in assigning NMR spectra where necessary.

MS: Low resolution mass spectra were recorded by the technical staff at the University of Bristol on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI), with only molecular ions of interest ($[\text{M}]^+$, $[\text{M} + \text{H}]^+$, $[\text{M} + \text{Na}]^+$) reported.

HRMS: High resolution mass spectra were recorded by the technical staff at the University of Bristol on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI).

Optical Rotations: ($[\alpha]_{\text{D}}^{25}$) Optical rotations were measured on a Bellingham and Stanley Ltd. ADP220 polarimeter using a cell with a pathlength of 0.25 dm with the solvent quoted and concentration (c) given in g/100 mL.

X-Ray Sample Preparation: Crystals suitable for X-ray were grown by dissolving the sample in a dense solvent (CH_2Cl_2) in which it is reasonably soluble which is then placed inside a second chamber containing a less dense solvent (Hexane or *n*-Pentane). The solvents slowly mixed together, altering the polarity of the solution in which the sample is dissolved, leading to crystallisation.

Precursors: All esters, amides, and imines (precursors to the *N*-chloroformylimidazolidinones) were synthesised on 10-30 gram scale according to our previously reported literature protocols.¹⁵⁻¹⁷

General Procedure 1: Synthesis of *trans* *N*-chloroformylimidazolidinones

The synthesis of *N*-chloroformylimidazolidinones on 10-30 gram scale according to our optimised method was previously reported.¹⁶⁻¹⁷ Phosgene solution (15% wt. in toluene, 1.5 equiv.) (handle carefully!) was added dropwise to a solution of the imine (1 equiv.) in dry THF (0.5 M) at room temperature under N_2 over approximately 30 min. A precipitate is typically observed 10-15 min after addition. After 2 h, pyridine (2 equiv.) was added dropwise. After stirring for a further 30-60 min, aqueous HCl (10 mL, 1.0 M) was added. The mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 and washed with aqueous HCl (1.0 M). The aqueous solution was further extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. Purifications by flash col-

umn chromatography or recrystallisation yielded the *trans* *N*-chloroformylimidazolidinone **2**. NOTE: Highly toxic phosgene solutions must be handled inside the fumehood. Needles and used glassware should be quenched with 1 M aqueous HCl inside the fumehood.

General Procedure 2: Alkylation of *N*-chloroformylimidazolidinones

A solution of *N*-chloroformylimidazolidinone (1.0 mmol) in THF (10.0 mL) was degassed by bubbling with N₂ for 15 min and cooled to -78 °C. KHMDS (1.1 mL, 1.1 mmol, 1.1 equiv., 1.0 M in THF) was added dropwise. After stirring for 5 min, the alkyl halide (1.1 mmol, 1.1 equiv.) was added dropwise. After stirring for 2 h at -78 °C, the reaction was quenched with water (10.0 mL). The mixture was extracted with EtOAc (2 x 10.0 mL). The combined organic layers were washed with brine (2 x 10.0 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to yield the alkylated product **3**.

General Procedure 3: Hydrolysis of alkylated *N*-chloroformylimidazolidinones

The *N*-chloroformylimidazolidinone **3** (1.0 equiv.) was dissolved in a mixture of trifluoroacetic acid and 6.0 M HCl (1:4 ratio, 0.05 M) in a microwave vial. 1 g of Dowex 50WX8 (prewashed sequentially with methanol and deionised water) was added to the reaction mixture. The sealed vial was heated in a microwave reactor at 130 °C (10-12 bar) for 4 h (reaction progress was monitored by TLC analysis). The reaction mixture was concentrated under reduced pressure. The Dowex resin (with adsorbed crude product) was washed with 20 mL of methanol, 50 mL of deionised water (to remove the methylamine hydrochloride byproduct), and finally 50 mL of 3% aqueous ammonia solution to elute the desired product. Concentration of the ammoniacal fractions under reduced pressure afforded the product.

General Procedure 4: CBz protection

In flask A, a solution of *trans* *N*-chloroformylimidazolidinone (1.0 mmol, 1.0 equiv.) in THF (0.2M) was degassed by bubbling with N₂ for 15 min and cooled to 0 °C. In flask B, NaH (60% suspension in mineral oil, 1.05 equiv.) was added to a solution of benzyl alcohol (1.1 equiv.) in dry THF (2 mL) at 0 °C. The solution was stirred for 30 minutes at 0 °C. The content of flask A was added to flask B dropwise over 10 min at 0 °C. The reaction mixture was warmed to RT and allowed to stir for 1 h. The reaction was quenched with water (10.0 mL). The mixture was extracted with EtOAc (2 x 10.0 mL). The combined organic layers were washed with brine (2 x 10.0 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to yield the desired product.

(2*S*,5*S*)-5-Benzyl-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (**2a**)

Following general procedure 1, the corresponding imine (24.83 g, 107.24 mmol) was dissolved in dry THF (220 mL) and treated with phosgene solution (133.10 mL, 160.87 mmol), followed by pyridine (13.24 mL, 163.845 mmol). After acidic work-up, the crude product (>99:1 *trans*:*cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to yield the title compound (29.10 g, 90%) as a white solid. Data in agreement with our previously reported values.¹⁵

(2*S*,5*S*)-5-(4-(Benzyloxy)benzyl)-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (**2b**)

Following general procedure 1, the corresponding imine (28.78 g, 82.02 mmol) was dissolved in dry THF (163 mL) and treated with phosgene solution (94.97 mL, 122.61 mmol), followed by pyridine (14.39 mL, 162.61 mmol). After acidic work-up, the crude product (>99:1 *trans*:*cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to afford the title compound (26.70 g, 81%) as a white solid. Data in agreement with our previously reported values.¹⁵

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(3,4-dimethoxybenzyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (**2c**)

Following general procedure 1, the corresponding imine (21.56 g, 70.40 mmol) was dissolved in dry THF (140 mL) and treated with phosgene solution (80.59 mL, 105.55 mmol), followed by pyridine (5.8 mL, 140.80 mmol). After acidic work-up, the crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 1:2) to afford the title compound (18.43 g, 85%) as a beige solid. Data in agreement with our previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(3-fluorobenzyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (2d)

Following general procedure 1, the corresponding imine (13.30 g, 50.33 mmol) was dissolved in dry THF (98 mL) and treated with phosgene solution (58.94 mL, 75.2677 mmol), followed by pyridine (7.60 mL, 100.51 mmol). The crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to afford the title compound (1.70 g, 82%) as a white solid. Data in agreement with our previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-5-(4-nitrobenzyl)-4-oxoimidazolidine-1-carbonyl chloride (2e)

Following general procedure 1, the corresponding imine (2.60 g, 9.36 mmol) was dissolved in dry THF (17.70 mL) and treated with phosgene solution (10.77 mL, 14.04 mmol), followed by pyridine (0.74 mL, 18.57 mmol). After acidic work-up, the crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to afford the title compound (2.5 g, 77%) as a white solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-5-(naphthalen-1-ylmethyl)-4-oxoimidazolidine-1-carbonyl chloride (2f)

Following general procedure 1, the corresponding imine (5.80 g, 20.73 mmol) was dissolved in dry THF (41 mL) and treated with phosgene solution (43.50 mL, 31.11 mmol), followed by pyridine (0.70 mL, 8.58 mmol). After acidic work-up, the crude product (97:3 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 2:1) to yield the title compound (5.50 g, 74%) as a beige solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-5-(naphthalen-2-ylmethyl)-4-oxoimidazolidine-1-carbonyl chloride (2g)

Following general procedure 1, the corresponding imine (2.28 g, 7.70 mmol) was dissolved in dry THF (15 mL) and treated with phosgene solution (9 mL, 11.58 mmol), followed by pyridine (1.25 mL, 15 mmol). After acidic work-up, the crude product (96:4 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 2:1) to yield the title compound (2.00 g, 73%) as a yellow solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-4-oxo-5-phenethylimidazolidine-1-carbonyl chloride (2h)

Following general procedure 1, the corresponding imine (2.90 g, 11.14 mmol) was dissolved in dry THF (23 mL) and treated with phosgene solution (9.00 mL, 16.80 mmol), followed by pyridine (1.86 mL, 22.3 mmol). After acidic work-up, the crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to yield the title compound (2.90 g, 83%) as a colourless solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(furan-2-ylmethyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (2i)

Following general procedure 1, the corresponding imine (0.84 g, 3.57 mmol, 1.0 eq.) was dissolved in dry THF (7.00 mL) and treated with phosgene solution (4.032 mL, 5.352 mmol), followed by pyridine (0.59 mL, 7.15 mmol). After acidic work-up, the crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to afford the title compound (0.83 g, 83%) as a beige solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-4-oxo-5-(thiophen-2-ylmethyl)imidazolidine-1-carbonyl chloride (2j)

Following general procedure 1, the corresponding imine (2.10 g, 8.53 mmol) was dissolved in dry THF (16 mL) and treated with phosgene solution (9.60 mL, 12.60 mmol), followed by pyridine (1.34 mL, 16.71 mmol). After acidic work-up, the

crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to afford the title compound (1.90 g, 73%) as a colourless solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-4-oxo-5-(thiophen-3-ylmethyl)imidazolidine-1-carbonyl chloride (2k)

Following general procedure 1, the corresponding imine (0.58 g, 2.3 mmol) was dissolved in dry THF (4.6 mL, 0.5 M) and treated with phosgene solution (2.64 mL, 3.45 mmol), followed by pyridine (0.37 mL, 4.60 mmol). After acidic work-up, the crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 6:1) to afford the title compound (0.56 g, 78%) as a white solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-4-oxo-5-((1-tosyl-1*H*-indol-3-yl)methyl)imidazolidine-1-carbonyl chloride (2l)

Following general procedure 1, the corresponding imine (2.46 g, 5.60 mmol) was then dissolved in dry THF (11.2 mL) and treated with phosgene solution (6.5 mL, 8.39 mmol), followed by pyridine (0.91 mL, 11.19 mmol). After acidic work-up, the crude product (96:4 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂; pet. ether/EtOAc 90:10 → pet. ether/EtOAc 20:80) to afford the title compound (2.44 g, 82%) as a white solid. Data in agreement with previously reported values.¹⁸

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-4-oxo-5-phenylimidazolidine-1-carbonyl chloride (2m)

Following general procedure 1, the corresponding imine (9.12 g, 41.60 mmol) was dissolved in dry THF (80 mL) and treated with phosgene solution (42 mL, 63.40 mmol), followed by pyridine (7.2 mL, 84.80 mmol). After acidic work-up, the crude product (>99:1 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 2:1) to yield the title compound (3.54 g, 72%) as a colourless solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (2n)

Following general procedure 1, the corresponding imine (30.00 g, 176.25 mmol) was dissolved in dry THF (352 mL) and treated with phosgene solution (200 mL, 39.00 mmol), followed by pyridine (28 mL, 352.50 mmol). After acidic work-up, the crude product (98:2 *trans:cis* diastereomeric ratio by ¹H NMR) was purified by recrystallisation from Et₂O/n-Hexane (1:1) to afford the title compound (35.2 g, 88%) as a white crystalline solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-5-isobutyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (2o)

Following general procedure 1, the corresponding imine (4.30 g, 20.24 mmol) was dissolved in dry THF (40.3 mL) and treated with phosgene solution (23.35 mL, 30.35 mmol), followed by pyridine (3.27 mL, 40.47 mmol). After acidic work-up, the crude product (> 95:5 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂; pet. ether/EtOAc 93:7 → pet. ether/EtOAc 40:60) to afford the title compound (4.18 g, 74%) as a white crystalline solid. Data in agreement with previously reported values.¹⁵

(2*S*,5*S*)-2-(*tert*-Butyl)-5-isopropyl-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (2p)

Following general procedure 1, the corresponding imine (1.20 g, 6.05 mmol) was dissolved in dry THF (12.10 mL) and treated with phosgene solution (6.98 mL, 9.08 mmol), followed by pyridine (0.98 mL, 12.10 mmol). The crude product was recrystallized using PE/Et₂O/CH₂Cl₂ to give the title compound (1.07 g, 68%) as an off-white crystalline solid. Data in agreement with previously reported values.¹⁵

(2*S*,5*S*)-5-Allyl-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (2q)

Following general procedure 1, the corresponding imine (2.85 g, 14.52 mmol) was dissolved in dry THF (29 mL) and treated with phosgene solution (16.80 mL, 21.78 mmol), followed by pyridine (2.3 mL, 29 mmol, 2.0 eq.). After acidic work-up,

the crude (>95:5 *trans:cis* diastereomeric ratio by ¹H NMR) was chromatographed (SiO₂, pet.ether/EtOAc, 4:1) to afford the title compound (3.42 g, 90%) as a pale yellow solid. Data in agreement with previously reported values.¹⁶

(2*S*,5*S*)-2-(*tert*-Butyl)-3-methyl-5-(2-(methylthio)ethyl)-4-oxoimidazolidine-1-carbonyl chloride (2r)

Following general procedure 1, the corresponding imine (570 mg, 2.47 mmol) was then dissolved in dry THF (4.95 mL) and treated with phosgene solution (2.85 mL, 3.71 mmol), followed by pyridine (0.40 mL, 4.95 mmol). After acidic work-up, the *trans* *N*-chloroformylimidazolidinone (697 mg, 95%, >95:5 *trans:cis* diastereomeric ratio by ¹H NMR) was obtained as an orange oil and used without further purification. Data in agreement with previously reported values.¹⁸

(2*S*,5*R*)-5-Allyl-5-benzyl-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (3a)

Following general procedure 2, *N*-chloroformylimidazolidinone **2a** (200 mg, 0.65 mmol), KHMDS (0.77 mL, 0.77 mmol, 1.2 equiv., 1.0 M in THF) and allyl bromide (0.17 mL, 1.95 mmol, 3 equiv.) gave, after purification by automated FC (SiO₂, pet.ether/EtOAc, 6:1), the title compound (180 mg, 86%) as a white solid. **mp**: 80-82 °C, **R_f** = 0.45 (pet.ether/EtOAc = 6:1); [α]_D²⁵ = -104 (*c* = 1 in CHCl₃); **IR** ν_{max} = 2974 (C-H), 1737(C=O), 1712 (C=O); **¹H NMR** (500 MHz, CDCl₃) (mixture of rotamers in a 0.52:0.48 ratio) δ 7.37 – 7.33 (m, 1H), 7.30 – 7.08 (m, 4H), 5.55 – 5.47 (m, 0.48H), 5.47 – 5.31 (m, 0.52H), 5.27 – 5.22 (m, 0.96H), 5.20 – 5.12 (m, 1.04H), 5.02 (s, 0.48H), 4.95 (s, 0.52H), 3.55 (d, *J* = 14.2 Hz, 0.96H), 3.35 (d, *J* = 14.2 Hz, 1.04H), 3.27 (dt, *J* = 14.4, 7.7 Hz, 0.52H), 3.10 (dd, *J* = 14.4, 7.7 Hz, 0.52H), 2.97 (s, 1.44H), 2.94 (d, *J* = 1.1 Hz, 1.56H), 2.67 (dd, *J* = 14.4, 7.7 Hz, 0.48H), 2.45 (dd, *J* = 14.0, 5.9 Hz, 0.48H), 0.81 (s, 4.32H), 0.56 (s, 4.68H). **¹³C {¹H} NMR** (125 MHz, CDCl₃) δ 170.5, 170.4, 150.1, 147.8, 135.7, 135.6, 131.3, 131.2, 130.5, 130.1, 128.6, 128.5, 127.5, 127.4, 121.9, 121.7, 83.3, 83.2, 73.8, 71.9, 43.0, 42.0, 41.3, 39.3, 38.4, 38.3, 31.4, 31.3, 27.4, 26.5. **HRMS** C₁₉H₂₅ClN₂O₂ [*M* + *H*]⁺ calculated: 349.1677, found: 349.1671.

(2*R*,5*R*)-5-Benzyl-2-(*tert*-butyl)-5-(4-chlorobenzyl)-3-methyl-4-oxoimidazolidine-1-carbonyl chloride (3b)

Following general procedure 2, *N*-chloroformylimidazolidinone *cis*-**2b**¹⁵ (200 mg, 0.65 mmol, 1.0 equiv.), KHMDS (0.77 mL, 0.77 mmol, 1.2 equiv., 1.0 M in THF) and 4-chlorobenzyl bromide (146 mg, 0.71 mmol, 1.1 equiv.) gave, after purification by automated FC (SiO₂, pet.ether/EtOAc, 4:1), the title compound (200 mg, 73%) as a colourless solid. **mp**: 127-129 °C, **¹H NMR** (500 MHz, CDCl₃) (mixture of rotamers in a 0.55:0.45 ratio) δ 7.43 – 7.39 (m, 1H), 7.36 – 7.32 (m, 1H), 7.30 – 7.27 (m, 2H), 7.26 – 7.21 (m, 3H), 7.14 – 7.06 (m, 2H), 4.34 (s, 0.55H), 4.15 (s, 0.45H), 3.75 (dd, *J* = 19.3, 14.2 Hz, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 3.53 – 3.44 (m, 2H), 3.16 (d, *J* = 14.2 Hz, 0.55H), 3.00 (d, *J* = 14.0 Hz, 0.55H), 2.70 (s, 1.65H), 2.62 (s, 1.35H), 0.68 (s, 4.95H), 0.39 (s, 4.05H). **¹³C {¹H} NMR** (125 MHz, CDCl₃) δ 169.8, 169.6, 149.3, 148.2, 135.6, 135.6, 133.9, 133.5, 133.1, 132.8, 131.9, 131.7, 131.4, 131.4, 128.8, 128.7, 128.6, 128.5, 127.7, 127.6, 82.8, 82.7, 75.3, 73.7, 43.2, 42.1, 41.4, 39.8, 38.5, 38.4, 31.3, 31.3, 27.4, 26.5. **HRMS** C₂₃H₂₆Cl₂N₂O₂ [*M* + *H*]⁺ calculated: 433.1444, found: 433.1464.

(2*S*,5*R*)-5-Benzyl-2-(*tert*-butyl)-3-methyl-5-(2-methylallyl)-4-oxoimidazolidine-1-carbonyl chloride (3c)

Following general procedure 2, *N*-chloroformylimidazolidinone **2a** (150 mg, 0.49 mmol), KHMDS (1M in THF, 0.53 mL, 0.53 mmol), and 3-bromo-2-methylprop-1-ene (73 μ L, 0.73 mmol) gave, after purification by FCC (SiO₂; pet. ether/EtOAc 90:10 \rightarrow pet. ether/EtOAc 80:20), the title compound (119 mg, 67%) as a white solid. **mp**: 87-89 °C, **R_f** 0.32 (SiO₂; pet. ether/EtOAc 80:20); [α]_D²⁴ = -120° (*c* = 1 in CHCl₃); **IR** (*neat*, cm⁻¹): ν_{max} 2968 (C-H), 1738 (C=O), 1712 (C=O); **¹H NMR** (400 MHz, CDCl₃) (mixture of rotamers in a 0.53:0.47 ratio) δ 7.45 – 7.12 (m, 5H), 5.10 – 4.70 (m, 3H), 3.55 (d, *J* = 14.0 Hz, 0.53H), 3.41 – 3.24 (m, 2H), 3.16 (d, *J* = 14.2 Hz, 0.47H), 2.97 (s, 1.41H), 2.92 (s, 1.59H), 2.62 (d, *J* = 14.4 Hz, 0.53H), 2.41 (d, *J* = 14.2 Hz, 0.47H), 1.61 (m, 3H), 0.85 (s, 4.3H), 0.58 (s, 4.7H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 170.5, 170.4, 149.8, 147.7, 139.3, 139.0, 135.7, 135.6, 131.5, 131.4, 128.6, 128.4, 127.6, 127.4, 118.4, 117.8, 83.1, 73.0, 71.3, 45.5, 42.9, 42.4, 42.2, 38.6, 31.7, 31.6, 27.6, 26.8, 23.2; **HRMS** C₂₀H₂₈ClN₂O₂ [*M*+*H*]⁺ calculated: 363.1834, found 363.1826.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-ethyl-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (3d)

Following general procedure 2, *N*-chloroformylimidazolidinone **2n** (150 mg, 0.65 mmol, 1.0 equiv.), KHMDS (0.77 mL, 0.77 mmol, 1.2 equiv., 1.0 M in THF) and ethyl iodide (0.26 mL, 3.25 mmol, 5 equiv.) gave, after purification by automated FC (SiO₂, pet.ether/EtOAc, 4:1), the title compound (141 mg, 85%) as a colourless oil. *R*_f = 0.36 (pet.ether/EtOAc = 4:1); [α]_D²⁵ = -116 (*c* = 1 in CHCl₃); IR ν_{max} = 2974 (C-H), 1737 (C=O), 1712 (C=O); ¹H NMR (500 MHz, CDCl₃) δ 5.18 (s, 0.51H), 5.16 (s, 0.49H), 3.02 (s, 1.47H), 3.01 (s, 1.53H), 2.49 (dq, *J* = 14.7, 7.4 Hz, 0.51H), 2.35 (dq, *J* = 14.7, 7.4 Hz, 0.49H), 1.94 (dq, *J* = 14.8, 7.4 Hz, 0.51H), 1.77 (dq, *J* = 14.6, 7.3 Hz, 0.49H), 1.63 (s, 1.53H), 1.56 (s, 1.47H), 1.08 (s, 4.59H), 1.00 (s, 4.41H), 0.63 (t, *J* = 7.4 Hz, 1.53H), 0.59 (t, *J* = 7.3 Hz, 1.47H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ 172.4, 172.2, 149.2, 145.7, 83.3, 82.9, 69.7, 67.7, 39.6, 39.2, 32.0, 31.7, 31.4, 28.9, 27.6, 26.9, 23.4, 22.7, 8.0. HRMS C₁₂H₂₂ClN₂O₂ [M + H]⁺ calculated: 261.1364, found: 261.1372. The relative stereochemistry was assigned by NOE experiments (See Supporting Information).

(2*S*,5*S*)-2-(*tert*-Butyl)-3,5-dimethyl-4-oxo-5-(prop-2-yn-1-yl)imidazolidine-1-carbonyl chloride (3e)

Following general procedure 2, *N*-chloroformylimidazolidinone **2n** (100 mg, 0.43 mmol), KHMDS (1M in THF, 0.47 mL, 0.47 mmol) and propargyl bromide (80% in toluene, 53 μ L, 0.47 mmol) gave, after purification by automated FC (SiO₂; pet. ether/Et₂O 85:15 \rightarrow pet. ether/Et₂O 0:100), the title compound (72 mg, 62%) as a colourless oil. *R*_f 0.33 (SiO₂; pet. ether/Et₂O 50:50); [α]_D²⁴ = -40 (*c* = 0.5 in CHCl₃); IR (neat, cm⁻¹): ν_{max} 2968 (C-H), 1738 (C=O), 1716 (C=O); ¹H NMR (400 MHz, CDCl₃) (mixture of rotamers in a 0.50:0.50 ratio) δ 5.23 (s, 0.5H), 5.21 (s, 0.5H), 3.38 (dd, *J* = 17.3, 2.7 Hz, 0.5H), 3.28 (dd, *J* = 16.9, 2.6 Hz, 0.5H), 3.07 (m, 3H), 2.87 (dd, *J* = 17.3, 2.7 Hz, 0.5H), 2.68 (dd, *J* = 16.9, 2.6 Hz, 0.5H), 2.03 (t, *J* = 2.6 Hz, 0.5H), 2.00 (t, *J* = 2.6 Hz, 0.5H), 1.65 (s, 1.5H), 1.58 (s, 1.5H), 1.10 (s, 4.5H), 1.02 (s, 4.5H); ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 171.7, 171.4, 148.6, 147.4, 84.0, 83.7, 78.2, 77.6, 72.8, 71.8, 68.6, 66.4, 39.5, 39.1, 32.2, 31.9, 30.2, 27.6, 27.3, 26.9, 22.6, 21.8; HRMS C₁₃H₁₉ClN₂O₂Na [M+Na]⁺ calculated: 293.1027, found 293.1036.

(2*S*,5*S*)-2-(*tert*-Butyl)-5-(4-chlorobenzyl)-3,5-dimethyl-4-oxoimidazolidine-1-carbonyl chloride (3f)

Following general procedure 2, *N*-chloroformylimidazolidinone **2n** (150 mg, 0.65 mmol), KHMDS (1M in THF, 0.77 mL, 0.77 mmol), and 4-chlorobenzyl bromide (146 mg, 0.72 mmol) gave, after purification by flash column chromatography, the title compound (170 mg, 74%) as a colourless foam. *R*_f = 0.23 (pet.ether/EtOAc 6:1). [α]_D²⁵ = -28 (*c* = 1 in CHCl₃); IR ν_{max} = 2983 (C-H), 1736 (C=O), 1709 (C=O); ¹H NMR (500 MHz, CDCl₃) δ 7.22 (dd, *J* = 8.6, 2.3 Hz, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 4.59 (s, 0.57H), 4.52 (s, 0.43H), 3.72 (d, *J* = 14.2 Hz, 0.43H), 3.59 (d, *J* = 14.0 Hz, 0.57H), 3.11 (d, *J* = 14.2 Hz, 0.43H), 3.02 (d, *J* = 14.0 Hz, 0.57H), 2.78 (s, 1.71H), 2.72 (s, 1.29H), 1.81 (s, 1.29H), 1.73 (s, 1.71H), 1.02 (s, 5.13H), 0.92 (s, 3.87H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ 171.5, 171.5, 148.3, 146.9, 133.7, 133.5, 133.4, 133.3, 131.6, 131.3, 128.6, 128.4, 82.8, 82.7, 70.5, 68.3, 42.8, 40.2, 39.9, 39.4, 31.8, 31.5, 27.7, 26.9, 23.7, 22.7. HRMS C₁₇H₂₃Cl₂N₂O₂ [M + H]⁺ calculated: 357.1131, found: 357.114325.

(2*S*,5*R*)-5-Allyl-2-(*tert*-butyl)-3-methyl-4-oxo-5-phenylimidazolidine-1-carbonyl chloride (3g)

Following general procedure 2, *N*-chloroformylimidazolidinone **2m**, KHMDS (0.61 mL, 0.61 mmol, 1.2 equiv., 1.0 M in THF) and allyl bromide (0.13 mL, 1.53 mmol, 3 equiv.) gave, after purification by automated FC (SiO₂, pet.ether/EtOAc, 6:1), the title compound (140 mg, 82%) as a colourless solid. mp: 113-115 °C, [α]_D²⁵ = +124 (*c* = 1 in CHCl₃); IR ν_{max} = 2974 (C-H), 1737 (C=O), 1712 (C=O); ¹H NMR (500 MHz, CDCl₃) (mixture of rotamers in a 0.90:0.10 ratio) δ 7.74 - 7.62 (m, 2H), 7.33 - 7.22 (m, 2H), 7.21 - 7.16 (m, 1H), 5.49 - 5.45 (m, 0.1H), 5.44 - 5.35 (m, 0.9H), 5.28 - 5.25 (m, 0.1H), 5.23 (s, 0.9H), 5.20 - 5.09 (m, 2H), 3.40 (dd, *J* = 14.5, 8.7 Hz, 0.1H), 3.31 (dd, *J* = 14.4, 8.8 Hz, 0.9H), 3.25 (ddt, *J* = 14.6, 5.9, 1.5 Hz, 0.1H), 3.00 (s, 2.7H), 2.96 (s, 0.3H), 2.82 (ddt, *J* = 14.4, 5.7, 1.5 Hz, 0.9H), 0.88 (s, 0.9H), 0.79 (s, 8.1H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ 170.2, 169.7, 150.8, 148.2, 139.4, 137.4, 131.1, 130.3, 128.5, 128.2, 128.1, 128.0, 128.0, 126.7, 126.1, 126.1, 122.1, 121.8, 84.2, 83.2, 74.6, 72.1, 44.8, 42.8, 39.3, 38.7, 31.9, 31.8, 27.2, 26.9. HRMS C₁₈H₂₄ClN₂O₂ [M + H]⁺ calculated: 335.152082, found: 335.152680. The relative stereochemistry was assigned by NOE experiments (See NOE section in Supporting Information).

(S)-2-Amino-2-methylbutanoic acid [L-Isovaline] (4)

Following general procedure 3, alkylated *N*-chloroformylimidazolidinone **3d** (50 mg, 0.19 mmol) was suspended in a mixture of TFA – 6.0 M HCl (1:4 ratio) (3.8 mL, 0.05 M) with Dowex 50WX8 (1 g) and heated in a microwave reactor at 130 °C (10 bar) for 4 h to afford the title compound (19 mg, 87%) as a white foam. $[\alpha]_D^{26} = +12$ ($c = 1$ in H₂O); ¹H NMR (500 MHz, CD₃OD) δ 1.93 (dq, $J = 15.1, 7.6$ Hz, 1H), 1.70 (dq, $J = 14.7, 7.5$ Hz, 1H), 1.44 (s, 3H), 0.98 (t, $J = 7.5$ Hz, 3H). ¹³C {¹H} NMR (125 MHz, CD₃OD) δ 175.1, 61.5, 30.5, 21.9, 7.2. Data in agreement with reported values in literature.¹⁹

(R)-2-Amino-2-benzyl-3-(4-chlorophenyl)-*N*-methylpropanamide(5)

Following general procedure 3, alkylated *N*-chloroformylimidazolidinone **3b** (50 mg, 0.11 mmol) was suspended in a mixture of TFA – 6.0 M HCl (1:4 ratio) (2.3 mL, 0.05 M) with Dowex 50WX8 (1 g) and heated in a microwave reactor at 130 °C (10 bar) for 4 h to afford the title compound (25 mg, 75%) as a white foam. $[\alpha]_D^{26} = -8$ ($c = 1$ in MeOH); IR $\nu_{\max} = 3325$ (NH₂ amide), 3291 (NH amide), 3315 (NH₂ amine), 2924 (C-H), 1689 (C=O amide); ¹H NMR (500 MHz, CD₃OD) δ 7.36 – 7.29 (m, 5H), 7.24 – 7.17 (m, 4H), 3.45 – 3.34 (m, 2H), 2.97 (dd, $J = 28.0, 14.2$ Hz, 1H), 2.70 (dd, $J = 13.1, 1.7$ Hz, 1H), 2.53 (s, 3H). ¹³C {¹H} NMR (101 MHz, CD₃OD) δ 177.7, 137.7, 136.7, 135.7, 134.6, 133.8, 133.1, 132.8, 131.6, 131.3, 129.8, 129.7, 129.3, 129.2, 128.6, 127.9, 63.9, 47.2, 46.4, 43.6, 42.8, 26.2. HRMS C₁₇H₁₉ClN₂O [M + H]⁺ calculated: 303.1259, found: 303.1256.

Benzyl (2*S*,5*S*)-5-benzyl-2-(*tert*-butyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (6)

Following general procedure 4, benzyl alcohol (0.14 mL, 0.71 mmol) in dry THF (1 mL), NaH (60% suspension in mineral oil, 39 mg, 0.71 mmol) and *N*-chloroformylimidazolidinone **2a** (200 mg, 0.65 mmol) in THF (3 mL) gave, after purification by automated FC (SiO₂; pet. ether/EtOAc 8:1 → pet. ether/ EtOAc, 3:1), the title compound (150 mg, 63%) as a colourless solid. R_f 0.06 (SiO₂; pet. ether/ EtOAc, 3:1); $[\alpha]_D^{25} = +12$ ($c = 1$ in CHCl₃); IR (neat, cm⁻¹): ν_{\max} 2968 (C-H), 1738 (C=O), 1716 (C=O); ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.30 (m, 3H), 7.25 – 7.15 (m, 7H), 5.07 (d, $J = 11.7$ Hz, 1H), 5.00 (s, 1H), 4.75 (s, 1H), 4.37 (t, $J = 6.5$ Hz, 1H), 3.23 (dd, $J = 13.7, 6.5$ Hz, 1H), 3.07 – 2.93 (m, 4H), 1.05 (s, 9H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ 171.2, 156.8, 138.1, 135.7, 130.2, 129.6, 128.6, 128.5, 128.4, 128.4, 126.6, 82.7, 67.9, 62.0, 39.9, 37.6, 31.5, 26.8. HRMS C₃₃H₂₉N₂O₃ [M + H]⁺ calculated: 381.2115, found: 381.2121. The relative stereochemistry was assigned by NOE experiments (See NOE section in Supporting Information). The structure and relative stereochemistry were also confirmed by X-ray crystallography after recrystallisation from dichloromethane and pentane.

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Supporting information: NMR characterization spectra for new compounds; VT NMR and Eyring data for conformational studies; X-ray crystal data; Additional details of optimization studies.

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